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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Heinz Kohler

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EXAMINER

HUYNH, PHUONG N

ART UNIT

PAPER NUMBER

1644

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,281	KOHLEK, HEINZ	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2004; 11/3/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 1-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/15/02</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-26 are pending.
2. Applicant's election with traverse of Group IX, Claims 21-26 drawn to a fusion protein made of an antibody and a peptide wherein the antibody is specific for cellular receptor that read on the species of idiotype antibody 3H1 and wherein the peptide is a specific binding site derived from natural ligand for a specific cellular receptor that read on the species of the complement fragment C3d and a composition comprising said fusion protein, filed 3/4/04, is acknowledged. The traversal is on the grounds that it is possible for some antibodies to be both specific for a membrane structure on a tumor cell or for a specific cellular receptor such as an anti-idiotypic antibody. The products of Groups IX and XII do not necessarily differ with respect to structure, physiochemical properties and effects. This is not found persuasive because of the reasons set forth in the restriction mailed 6/3/03. The claimed fusion protein made up of antibody and a specific peptide such as a specific binding site derived from natural ligand for a specific cellular receptor, a specific hormone, a specific ligand for a specific cytokine, or specific binding site derived from natural ligand for a specific cellular receptor. Although the antibodies may be both specific for a membrane structure on a tumor cell or for a specific cellular receptor such as an anti-idiotypic antibody, the fusion partners (peptide) in the fusion protein are not the same. In addition to having different structure, these fusion proteins have different function such as immunostimulatory, membrane transport homophilic activities. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group IX and Groups I-VIII and X-XII is still deemed proper and is therefore made FINAL.
3. Claims 1-20 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

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4. Claims 21-26 drawn to a fusion protein made of an antibody and a peptide wherein the antibody is specific for cellular receptor that read on the species of idiotypic antibody 3H1 and wherein the peptide is a specific binding site derived from natural ligand for a specific cellular receptor that read on the species of the complement fragment C3d and a composition comprising said fusion protein are being acted upon in this Office Action.

5. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/070,907, filed May 4, 1998, which is now Pat No. 6,238,667.

6. The abstract of the disclosure is objected to because it is too long. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of **50 to 150** words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a fusion protein comprising an anti-idiotypic anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhances the immunogenicity of the claimed anti-idiotypic antibody, **does not** reasonably provide enablement for any fusion protein as set forth in claims 21-26. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

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of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1. The peptide of SEQ ID NO: 1 is derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhances the immunogenicity of the anti-idiotypic antibody (See page 15-16). The anti-idiotypic antibody can be used as CEA antigen for making anti-CEA antibody.

The specification does not teach how to make and use all fusion protein made up of any antibody and any peptide without the amino acid sequence, and the corresponding nucleic acid encoding all undisclosed antibody and undisclosed peptide. There is insufficient guidance as to the structure of the peptide without the amino acid sequence, let alone the length of the peptide wherein the peptide has inverse hydropathicity, has immuno-stimulatory activity, membrane transport activity or homophilic binding activity. There is insufficient guidance as to which undisclosed peptide has immunostimulatory activity, which undisclosed peptide has membrane transport activity and which undisclosed peptide has "homophilic" activity. The examiner assumes that the "homophilic activity" is meant to be homophilic adhesion or binding activity. Further, there is insufficient guidance as to the binding specificity of the antibody, heavy or light chain immunoglobulin of the fusion protein, let alone which antibody that bind to all cellular receptors on which normal cell or on tumor cell.

With regard to fusion gene (claim 23), there is insufficient guidance as to the promoter, exons and introns of the "gene" that is used to create all fusion protein without the nucleic acid sequence.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). It has been well

known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

Given the indefinite number of undisclosed fusion protein comprising undisclosed antibody and peptide, it is unpredictable which peptide when fused to the antibody has which particular biological activity, in turn, would be useful for any purpose.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 21-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all fusion protein made up of any antibody, any antibody light chain or heavy chain immunoglobulin, any antibody specific for all cellular receptor on a normal cell or on tumor cell, any antibody is a full-length immunoglobulin or a variable domain fragment of said antibody fused to any peptide having a

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biological activity such as immuno-stimulatory, membrane transport or homophilic activities, or any peptide has inverse hydropathicity within the length of said peptide wherein the peptide is attached to the C-terminal or the N-terminal of the light chain or heavy chain at a site that does not interfere with the antigen binding of the antibody, and any fusion protein mentioned above creating by a fusion gene comprising any nucleic acid sequence encoding any antibody and peptide (claim 23).

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16).

With the exception of the specific fusion protein mentioned above, there is insufficient written description about the structure associated with function of the peptide in the fusion protein without the amino acid sequence, much less about the function such as which undisclosed has immuno-stimulatory activity, which undisclosed peptide has membrane transport activity and which undisclosed peptide has homophilic activity. There is insufficient written description about the binding specificity and function of the antibody in the fusion protein. There is insufficient written description about the structure associated with function of the nucleic acid sequence of the corresponding fusion protein made up of the undisclosed antibody and peptide. Further, it is not clear what is meant by "inverse hydropathicity".

With regard to "fusion gene" (claim 23), a gene encompasses exons, introns, and promoter. There is a lack of a written description about the promoter, exons and introns of the "gene" that is used to create all fusion protein without the nucleic acid sequence.

Finally, given the lack of an additional species of fusion protein made up of other antibody and other peptide in the specification as filed, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

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10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "homophilic activities" in claims 21 and 23 is ambiguous and indefinite because it is not clear what is meant by "homophilic activity". One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The preamble "The composition" in claims 24-26 has no antecedent basis in base claim 23 because the word "composition" is not recited in claim 23.

The "inverse hydropathicity" in claim 26 is indefinite and ambiguous because the specification does not define what is meant by "inverse hydropathicity". One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 21-23, and 25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,314,955 (May 1994, PTO 892).

The '955 patent teaches a fusion protein made up of an antibody such as anti-tumor antigen L6 antibody and peptides such as IL-2, and IL6 having a immunostimulatory activity such as lymphocyte proliferation (See column 2, line 38-42, summary of the invention, in particular). The reference IL-2 peptide is connected to a site such as the Fc region of the reference antibody that does not interfere the reference antibody from biding to tumor cells. The reference fusion protein is created by a process comprising the steps of creating a fusion gene comprising a nucleic acid sequence encoding the reference antibody and a nucleic acid sequence encoding the reference peptide (See Fig 6A-10, column 3, Construction of recombinant genes encoding antibody fusion proteins, in particular). The '955 patent teaches that the reference antibody is the variable region of the light and heavy chain of the anti-tumor antigen monoclonal

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antibody (See column 2, line 52, lines 55, in particular). The reference antibody based fusion proteins are useful as a method of delivering biologically active ligand molecules to the target cells or tissues and offers the advantage of decreasing systemic exposure to lymphokines and minimizing toxic effects (See column 8, lines 21-26, in particular). Claim 26 is included in this rejection because IL-2 is an immunogenic peptide that inherently has an inverse hydropathicity plot. Thus, the reference teachings anticipate the claimed invention.

14. Claims 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,698,679 (Dec 1997, PTO 1449).

The '679 patent teaches a fusion protein comprising an antibody that is specific for a cellular receptor such as CD40 on APC cells and B cells fused to an immunogenic peptide such as ovalbumin 326-337 (See entire document, column 25, example 2, column 8, lines 43-50, in particular). Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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17. Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,314,955 (May 1994, PTO 892) in view of Dempsey *et al* (Science 271: 348-350, 1996; PTO 1449), Tao *et al* (Nature 362(3622): 755-8, April 1993; PTO 892) and Bhattacharya-Chatterjee *et al* (J Immunology 145: 2758-2785, 1990; PTO 1449) or WO 96/20219 publication (July 1996, PTO 892).

The teachings of the '955 patent have been discussed supra.

The claimed invention in claims 21 and 23 differs from the teachings of the reference only in that the fusion protein is made up of an anti-idiotypic antibody 3H1 and the peptide is C3d that has immunostimulatory activity.

The invention in claim 24 differs from the teachings of the reference only in that the composition wherein the antibody is specific for a cellular receptor on a normal cell or a tumor cell.

Dempsey *et al* teach a fusion protein made up of hen egg lysozyme (HEL) and a peptide such as complement C3d peptide that has immuno-stimulatory activity such as antibody response to HEL (See entire document, Figure 1, Figure 3, in particular). Dempsey *et al* teach that peptide C3d is a molecular adjuvant of innate immunity and attaching C3d peptide to any antigen enhances the magnitude of antibody by as much as 10,000 fold (See page 350, column 1, in particular).

Tao *et al* teach vaccine against cancer, the antigens must preferentially expressed by tumor cells. Tao *et al* further teach idiotypic immunoglobulins are tumor specific but are weak immunogens (See abstract, in particular). To enhance immune response in animals or humans, the idiotypic protein has to be chemically coupled to a strongly immunogenic protein such as KLH and mixed with an adjuvant or fusing to GM-CSF to convert nonimmunogenic to a strong immunogen capable of inducing idiotypic specific antibody response (See abstract, in particular).

Bhattacharya-Chatterjee *et al* teach an anti-idiotypic antibody such as 3H1 that elicits the production of anti-CEA antibody that binds specifically to carcinoembryonic antigen (CEA) on normal and tumor cell in colon carcinoma (See abstract, Materials and Methods on page 2759, page 2760, column 2, 2nd paragraph, page 2761, column 1, 2nd paragraph, in particular). Bhattacharya-Chatterjee *et al* teach antibody 3H1 appears to functionally mimics CEA antigen and has the potential to be used as a network antigen for CEA to induce anti-tumor immunity in GI cancer patients (See page 2759, column 1, first paragraph, in particular).

The WO 96/20219 publication teaches various antibody such as anti-idiotypic antibody 3H1 that elicits specific antibody response to CEA in various species such as mice, rabbits and monkeys and humans associated with advanced CEA associated disease (See abstract, in particular). The WO 96/20219 publication teaches a pharmaceutical composition comprising the reference antibody and a pharmaceutically acceptable excipient and/or adjuvant for eliciting immune response with advanced CEA associated disease (See claims 7-13 of WO 96/20219 publication). The WO 96/20219 publication teaches the reference antibody 3H1 can be used as a CEA antigen substitute to induce anti-tumor immunity in gastrointestinal cancer patients with advanced CEA associated disease because immunization with intact CEA molecule might trigger potentially harmful autoimmune reactions (See paragraph bridging pages 4 and 5, lines 1-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody and the peptide in the fusion protein as taught by the '955 patent for the anti-idiotypic antibody such as 3H1 as taught by Bhattacharya-Chatterjee *et al* or the WO 96/20219 publication and the IL2 peptide for the GM-CSF peptide as taught by Tao *et al* or the C3d peptide as taught by Dempsey *et al* for a fusion protein made up of anti-idiotypic antibody such as 3H1 and GM-CSF or C3d peptide. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine the references because Tao *et al* teach idiotypic immunoglobulin are tumor specific but are weak immunogens (See abstract, in particular). To enhance immune response in animals or humans, the idiotypic protein has to be chemically coupled to a strongly immunogenic protein such as KLH and mixed with an adjuvant or fusing to GM-CSF to convert nonimmunogenic to a strong immunogen capable of inducing idiotypic specific antibody response (See abstract, in particular). Dempsey *et al* teach that peptide C3d is a molecular adjuvant of innate immunity and attaching C3d peptide to any antigen enhances the magnitude of antibody by as much as 10,000 fold (See page 350, column 1, in particular). Bhattacharya-Chatterjee *et al* teach an anti-idiotypic antibody such as 3H1 elicits the production of anti-CEA antibody that binds specifically to carcinoembryonic antigen (CEA) on normal and tumor cell in colon carcinoma. Bhattacharya-Chatterjee *et al* teach antibody 3H1 appears to functionally mimics CEA and has the potential to be used as a network antigen for CEA to induce anti-tumor immunity in GI cancer patients (See page 2759, column 1,

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first paragraph, in particular). The WO 96/20219 publication teaches the reference antibody 3H1 can be used as antigen CEA substitute to induce anti-tumor immunity in gastrointestinal cancer patients with advanced CEA associated disease because immunization with intact CEA molecule might trigger potentially harmful autoimmune reactions (See paragraph bridging pages 4 and 5, lines 1-12, in particular). The '955 patent teaches fusion protein made up of an antibody and peptides such as IL-2, IL6 has a immunostimulatory activity such as lymphocyte proliferation (See column 2, line 38-42, summary of the invention, in particular). Claim 26 is included in this rejection because the immunogenic C3d peptide would have been expected to be hydrophilic or inverse hydropathicity within the length of the peptide.

18. Claims 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,314,955 (May 1994, PTO 892) in view of Rojas *et al* (J Biol Chem 271(44): 27456-61, 1996; PTO 892) and Bhattacharya-Chatterjee *et al* (J Immunology 145: 2758-2785, 1990; PTO 1449) or WO 96/20219 publication (July 1996, PTO 892).

The teachings of the '955 patent have been discussed supra.

The claimed invention in claims 21 and 23 differs from the teachings of the reference only in that the fusion protein made up of an anti-idiotypic antibody 3H1 and the peptide has membrane transport activity.

Rojas *et al* teach a fusion protein comprising a cell membrane translocating sequence AAVALLPAVLLALLAP fused to phosphopeptide (See Figure 1, page 27457, column 1, in particular). Rojas *et al* teach by introducing functionally distinct domains such as the reference cell membrane translocating peptide in the fusion protein, this peptide would function as a carrier and would have been expected to deliver various cargo into the cell, which is useful for designing therapeutic molecular drugs for tumors related to oncogenes (See page 27461, column 1, in particular).

Bhattacharya-Chatterjee *et al* teach an anti-idiotypic antibody such as 3H1 that elicits the production of anti-CEA antibody that binds specifically to carcinoembryonic antigen (CEA) on normal and tumor cell in colon carcinoma (See abstract, Materials and Methods on page 2759, page 2760, column 2, 2nd paragraph, page 2761, column 1, 2nd paragraph, in particular). Bhattacharya-Chatterjee *et al* teach antibody 3H1 appears to functionally mimics CEA antigen and has the potential to be used as a network antigen for CEA to induce anti-tumor immunity in GI cancer patients (See page 2759, column 1, first paragraph, in particular).

The WO 96/20219 publication teaches various antibody such as anti-idiotypic antibody 3H1 that elicits specific antibody response to CEA in various species such as mice, rabbits and monkeys and humans associated with advanced CEA associated disease (See abstract, in particular). The WO 96/20219 publication teaches a pharmaceutical composition comprising the reference antibody and a pharmaceutically acceptable excipient and/or adjuvant for eliciting immune response with advanced CEA associated disease (See claims 7-13 of WO 96/20219 publication). The WO 96/20219 publication teaches the reference antibody 3H1 can be used as a CEA antigen substitute to induce anti-tumor immunity in gastrointestinal cancer patients with advanced CEA associated disease because immunization with intact CEA molecule might trigger potentially harmful autoimmune reactions (See paragraph bridging pages 4 and 5, lines 1-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody and the peptide in the fusion protein as taught by the '955 patent for the anti-idiotypic antibody such as 3H1 as taught by Bhattacharya-Chatterjee *et al* or the WO 96/20219 publication fused to the peptide that has membrane translocating activity as taught by Rojas *et al* for a fusion protein made up of anti-idiotypic antibody such as 3H1 and peptide with transport activity. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine the references because Rojas *et al* teach by introducing functionally distinct domains such as the reference cell membrane translocating peptide in the fusion protein, this peptide would function as a carrier and would have been expected to deliver various cargo into the cell such as tumors (See page 27461, column 1, in particular). Bhattacharya-Chatterjee *et al* teach an anti-idiotypic antibody such as 3H1 elicits the production of anti-CEA antibody that binds specifically to carcinoembryonic antigen (CEA) on normal and tumor cell such as colon carcinoma. Bhattacharya-Chatterjee *et al* teach antibody 3H1 appears to functionally mimics CEA antigen and has the potential to be used as a network antigen for CEA to induce anti-tumor immunity in GI cancer patients (See page 2759, column 1, first paragraph, in particular). The WO 96/20219 publication teaches the reference antibody 3H1 can be used as antigen CEA substitute to induce anti-tumor immunity in gastrointestinal cancer patients with advanced CEA associated disease because immunization with intact CEA molecule might trigger potentially harmful autoimmune reactions (See paragraph

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bridging pages 4 and 5, lines 1-12, in particular). The '955 patent teaches fusion proteins are useful as a method of delivering biologically active ligand molecules to the target cells with the advantage of decreasing systemic exposure to lymphokines and minimizing toxic effects (See column 8, lines 21-26, in particular).


19. No claim is allowed.
20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.
21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

May 14, 2004


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